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Atherosclerotic and Thrombogenic Neointima Formed Over Sirolimus Drug-Eluting Stent

An Angioscopic Study

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OBJECTIVES We sought to examine by angioscopy the neointima formation and thrombogenic potential of the neointima after deployment of a drug-eluting stent (DES).

BACKGROUND Late stent thrombosis after DES implantation, a major safety concern, has been associated with poor strut coverage by neointima. Intracoronary angioscopy provides a method for visual evaluation of stent coverage by neointima and detection of thrombus in the stented coronary segment.

METHODS Patients undergoing implantation of a sirolimus DES (n = 57) were serially examined by angioscopy immediately after (baseline) and again at 10 months (follow-up) after implantation. The angioscopic color grade of the neointima from white to yellow was assessed in a semiquantitative manner. Stent coverage was classified into not covered (Grade 0), covered by a thin layer (Grade 1), or buried under neointima (Grade 2). The thrombogenic potential of the neointima was evaluated by the prevalence of thrombus on the neointima.

RESULTS The maximum yellow color grade of the neointima within DES-implanted lesions increased significantly from baseline to follow-up (1.4 ± 1.1 vs. 1.9 ± 0.6, p = 0.0008). Even among lesions without yellow color at baseline, yellow color was detected in 94% (17 of 18) of lesions at follow-up. The prevalence of thrombus was significantly higher on the yellow than on the white neointimal areas. Thrombus was detected on yellow and/or Grade-0/1 neointima, but never on the white Grade-2 neointima.

CONCLUSIONS Sirolimus DES promoted formation of atherosclerotic yellow neointima in the stent-implanted lesion at 10-month follow-up. Thrombus was detected more often on the yellow area than on the white area and was never detected where a stent was buried under white neointima. These data suggest that the increased potential risk of late stent thrombosis in DES lesions may be due to the newly formed yellow neotima and cholesterol-laden plaque. (J Am Coll Cardiol Img 2009;2:616–24)

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Drug-eluting stents (DES), a treatment of choice for patients with coronary heart disease undergoing percutaneous coronary intervention (PCI), dramatically reduce restenosis. DES have been associated with life-threatening late stent thrombosis more than bare-metal stents (BMS) (1). Pathological examinations (2) of patients dying of late DES thrombosis have revealed that delayed arterial healing, characterized by incomplete re-endothelization and persistent fibrin deposition, is an important underlying substrate for DES thrombosis. However, the process

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and characterization of neointima formation over DES and its role in the antithrombogenic function has not been fully clarified. Atherosclerotic change within the neointima after BMS implantation is a rare phenomenon and usually occurs beyond 5 years. This observation has not been reported in DES. The yellow color of coronary plaque seen by angioscopic examination is associated with lipid-rich atherosclerotic plaque and has a high thrombogenic potential (3,4). Therefore, to characterize the neointima in DES, we examined the neointima color, degree of strut coverage, and prevalence of thrombus by angioscopy after sirolimus DES implantation at baseline and late follow-up evaluation.

METHODS

Study patients. A series of patients who underwent PCI with Cypher (Cordis Corp., Johnson & Johnson Co., Warren, New Jersey) sirolimus DES were serially examined by angioscopy immediately (baseline) and at 10 ± 3 months (follow-up) after stent implantation. Stent thrombosis as a clinical event was not detected in any patient. Patients who underwent reintervention of the stented lesion before follow-up examination were excluded. Follow-up catheterization was prospectively planned for all patients who received PCI.

Patients (n = 12) who underwent implantation of BMS and follow-up angioscopic examination were included retrospectively as a reference.

Intravenous heparin (100 U/kg) was administered at the beginning of catheterization, and an additional dose was repeated at the time of PCI as a routine protocol in our hospital. Stent implantation was guided by intravascular ultrasound imaging to achieve appropriate implantation. Antiplatelet therapy was oral ticlopidine (200 mg/day, >3 months [DES] or >1 month [BMS]) and aspirin (81 to 200 mg/day). New antiplatelet agents, clopidogrel, or glycoprotein IIb/IIIa blockers, were not used because they were not approved in Japan.

Hypertensive patients were defined as those with blood pressure >140/90 mm Hg or those already taking antihypertensive drugs. Diabetic patients were defined as those with fasting blood glucose >126 mg/dl or those already taking oral drugs for diabetes mellitus or receiving insulin therapy. Obesity was defined as body mass index >26.4 kg/m^2. Acute coronary syndrome (ACS) included acute myocardial infarction with/without ST-segment elevation as defined by the Joint European Society of Cardiology/American College of Cardiology Committee and unstable angina was defined according to the Braunwald classification. DES were not implanted at the culprit lesion(s) of ACS but at additional sites of severe stenosis. Written informed consent was acquired from all patients. This protocol was approved by the Osaka Police Hospital Ethical Committee.

Angioscopic procedures and evaluations. Catheterization was performed by a femoral, brachial, or radial artery approach using a 6- or 7-F sheath and catheters. The coronary angiogram was recorded by the Advantx medical system (GE Yokogawa, Tokyo, Japan). The angioscope RX-3310A and MV-5010A (Machida, Tokyo, Japan) and optic fiber DAG-2218LN (Machida) were used. Angioscopic observations were made while blood was cleared away from view by the injection of 3% dextran-40 as previously reported (5). Stent coverage by neointima, lesion color, and thrombus at the stented lesion were evaluated by angioscopy. Lesion color was classified into 4 grades (0 = white, 1 = slight yellow, 2 = yellow, 3 = intensive yellow) compared with the standard colors as we have previously reported (3), and the maximum color grade was determined for each stented lesion. Stent coverage was classified into not covered (Grade 0), covered by thin layer (Grade 1), or buried under neointima (Grade 2), as previously reported (6). Maximum and minimum stent coverage was determined for each stented lesion. A stent that was buried under neointima (Grade 2) was identified as such if the stent strut was not visible under neointima or the stent strut was visible through the neointima but was below the level of neointima surface. A stent that was covered by a thin layer (Grade 1) was identified as such if the stent strut was visible on the vessel surface but was covered by a thin layer. Presence or absence of all combinations of stent

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
PCI = percutaneous coronary intervention

coverage, lesion color, and thrombus were judged for each stented lesion. Thrombus was defined as white or red material that had cotton-like or ragged appearance or that presented fragmentation with or without protrusion into the lumen or was adherent to the luminal surface. Because we previously reported (3) that a yellow lesion is more thrombogenic than a white lesion, we recorded the color of the lesion and thrombus adhering directly to the lesion. The neointima underlying any thrombus at the site of strut coverage was graded for the presence or absence of yellow plaque. Angioscopic evaluations were made by two angioscopic specialists blinded to patient characteristics and timing of examination (baseline or follow-up), and in case of disagreement, a third reviewer served as an arbitrator. Inter- and intraobserver reproducibilities for interpretation of angioscopic images (6) were 95% and 95%, respectively, for stent coverage (100% and 100%, respectively, for judging stent coverage of Grade 2 or not), 85% and 95%, respectively, for plaque color, and 90% and 100%, respectively, for thrombus.

Statistics. Continuous data were presented as mean ± SD. Comparisons were made between baseline and follow-up by using paired Student *t* test or Wilcoxon signed rank test. Subgroups were compared by unpaired Student *t* test or chi-square test. A value of $p < 0.05$ was regarded as statistically significant.

RESULTS

Angioscopic findings on neointima. Patient and lesion characteristics are presented in Tables 1 and 2, respectively. Neointima coverage (Fig. 1) of DES was poor. A majority of stents showed Grade 1 or less, and BMS had greater neointimal coverage, which is consistent with previous reports (6–9). The maximum yellow color grade of the stented lesion increased significantly (Fig. 2) from baseline to follow-up. There were subgroups of patients in whom maximum yellow color grade increased (42%), did not change (42%), or decreased (16%) from baseline to follow-up. Even among lesions without yellow plaque at baseline, yellow plaque was detected in 94% (17 of 18) of lesions at follow-up. Yellow plaque was detected at follow-up in the original vessel wall under the stent where the stent coverage was Grade 0 or 1, and was also detected in the newly formed neointima over the stent where the stent coverage was Grade 2. Grade-2 neointima newly formed over DES had atherosclerotic yellow plaque in 30% of lesions (33% of lesions even among those without yellow plaque at baseline). Yellow plaque was observed both in the newly formed neointima and in the original vessel wall after DES implantation. In contrast to DES, BMS had greater coverage predominantly by white Grade-2 neointima.

Table 1. Patient Characteristics

Characteristic	DES	BMS
Patients, n	57	12
Age, yrs	68 ± 9	61 ± 12
Male gender, n (%)	49 (86)	9 (75)
Acute coronary syndrome*	14 (25)	1 (8)
Prior MI	19 (33)	3 (25)
Number of diseased vessels		
1 vessel	29 (51)	9 (75)
2 vessels	21 (37)	2 (17)
3 vessels	7 (12)	1 (8)
Coronary risk factors		
Hypertension	42 (74)	6 (50)
Diabetes mellitus	20 (35)	3 (25)
Current smoking	11 (19)	4 (33)
Obesity	9 (16)	2 (17)
Serum lipid levels at baseline, mg/dl		
Total cholesterol	209 ± 37	195 ± 36
LDL cholesterol	121 ± 32	114 ± 29
HDL cholesterol	49 ± 13	51 ± 11
Triglyceride	159 ± 122	134 ± 78
Serum lipid levels at follow-up, mg/dl		
Total cholesterol	185 ± 30	193 ± 35
LDL cholesterol	101 ± 30	108 ± 33
HDL cholesterol	53 ± 15	52 ± 10
Triglyceride	140 ± 105	168 ± 117
Medications at baseline		
Aspirin†	53 (95)	10 (83)
Ticlopidine†	51 (89)	3 (25)
Statins	21 (37)	6 (50)
ACEI/ARB	23 (40)	2 (17)
Medications at follow-up		
Aspirin	53 (95)	12 (100)
Ticlopidine	41 (72)	4 (33)
Statins	38 (67)	8 (67)
ACEI/ARB	28 (49)	3 (27)
Follow-up interval, months	10 ± 3	6 ± 3

Unless indicated otherwise, data are given as n (%) or mean ± SD. *Acute coronary syndrome includes acute MI with/without ST-segment elevation defined by the Joint European Society of Cardiology/American College of Cardiology Committee, and unstable angina defined according to the Braunwald classification. †n (%) of patients who were already taking this drug before PCI; dual anti-platelet therapy with aspirin and ticlopidine was started as soon as decision was made to perform PCI.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMS = bare-metal stent(s); DES = drug-eluting stent(s); HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Angioscopic findings of thrombus. The prevalence of thrombus was higher on the yellow areas than on

Table 2. Lesion Characteristics

Characteristic	DES	BMS
Target vessel		
LAD	27 (47)	8 (67)
LCX	6 (11)	1 (8)
RCA	23 (40)	3 (25)
LMC	1 (2)	0 (0)
Lesion type*		
A	1 (2)	0 (0)
B1	6 (11)	0 (0)
B2	35 (61)	11 (92)
C	15 (26)	1 (8)
Lesion length, mm		
<10	3 (5)	0 (0)
10–20	40 (70)	11 (92)
>20	14 (25)	1 (8)
Restenotic lesion	5 (9)	0 (0)
CTO lesion	5 (9)	0 (0)
Stent size in diameter, mm	3.1 ± 0.4	3.2 ± 0.5
Total stent length, mm	25 ± 15	16 ± 3
Maximum inflation pressure, atm	15 ± 3	13 ± 4
Total inflation time, min	2 ± 5	2 ± 2
Diameter stenosis at follow-up, %	10 ± 18	23 ± 13

Unless otherwise indicated, data are given as n (%) or mean ± SD. *Lesion type according to American College of Cardiology/American Heart Association classification.
CTO = chronic total occlusion; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LMC = left main coronary artery; RCA = right coronary artery; other abbreviations as in Table 1.

the white areas at follow-up (Fig. 4). Thrombus was detected on yellow and/or Grade-0/1 neointima (Fig. 3). However, when stent strut coverage was white Grade-2 neointima, thrombus was never detected. All thrombi were mural, none was occlusive, and none was detectable by angiography. Among those who received BMS, thrombus was detected in only 1 patient in the area where the stent was not covered by neointima (Grade 0).

Representative angioscopic pictures of DES-implanted lesions are presented in Figure 5. Representative cases of yellow neointima formed over DES are presented in Figures 6 and 7.

DISCUSSION

Although DES have significantly reduced the rate of restenosis, late stent thrombosis has emerged as a serious problem. We previously reported (5,10) that angioscopic findings in BMS consist of gradual coverage by white neointima, with a reduced thrombogenic potential. Yellow plaque formation in neointima was never observed in BMS within 12 months of follow-up according to our experience and previous reports. In the present study, we demonstrated that DES are poorly covered by neointima at 10 months, a finding consistent with those in previous reports (6–9). In addition to poor neointimal coverage, Grade-2 neointima newly formed over DES had atherosclerotic yellow plaque in 30% of lesions (33% of lesions even among those without yellow plaques at baseline). Yellow plaque formation was also enhanced in the vessel wall underneath the stent after DES implantation. The area with yellow plaque was found to be more thrombogenic than the area without yellow plaque, and Grade-2 neointima without yellow plaque failed to show any thrombus.

Stent coverage by neointima and thrombogenic potential of the stented lesion. The healing process of a stented vessel has been widely investigated and reported (11–14) both for BMS and DES. The earliest change is the presence of thrombus followed by proliferation of smooth muscle cells and endothelial cells. In native coronary arteries, the thrombogenic potential after exposure of the lipid core is extremely high, and it is well known that coverage of the lipid core by thick fibrous tissue reduces the thrombogenic potential of the culprit lesion. Angioscopic studies of BMS (5,10) revealed that coverage of the stent struts by white smooth neointima is associated with absence of thrombus formation, especially after 12 months, suggesting that the neointima sealed the yellow plaque underneath the stent, thus stabilizing the lesion.

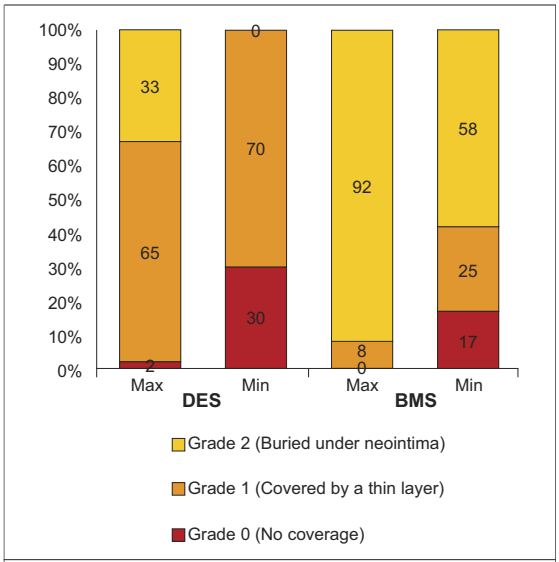

Figure 1. Maximum and Minimum Neointima Coverage of Stent Struts in DES and BMS at Follow-Up

Majority of neointima coverage was Grade 1 (covered by thin layer) in drug-eluting stents (DES), but was Grade 2 (buried under neointima) in bare-metal stents (BMS).

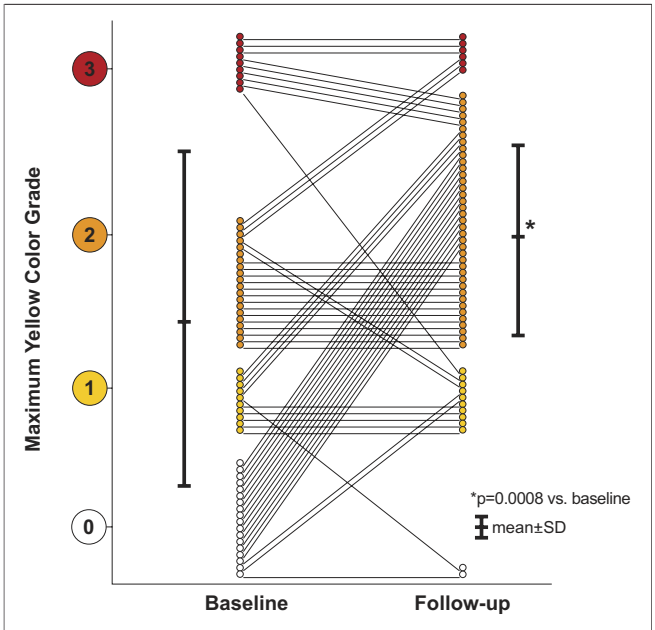

Figure 2. Changes in Maximum Yellow Color Grade From Baseline to Follow-Up in DES

Maximum yellow color grade increased significantly from baseline to follow-up after drug-eluting stent (DES) implantation (1.4 ± 1.1 vs. 1.9 ± 0.6, p = 0.0008).

Although the DES reduced the restenosis rate (15–24) by preventing smooth muscle cell proliferation, it increased the rate of stent thrombosis (1,25–28) after 1 year (very late stent thrombosis), a result rarely seen in BMS. Late stent thrombosis may be caused by the poorly formed neointima over DES that has failed to cover and stabilize underlying thrombogenic yellow plaque. In the present study, we showed that areas with yellow plaque are more thrombogenic than those without yellow plaque. Furthermore, we demonstrated for the first time that yellow plaque formation was promoted both in the newly formed neointima and in the original vessel wall underneath the DES at 10 months after implantation. On the other hand, yellow neointima was not observed within 1 year after BMS implantation. These newly formed yellow plaques appeared to have increased the thrombogenic potential of DES-implanted lesions. We noted a trend toward regression of yellow plaque with a reduction of thrombogenic potential (healing) and a trend toward progression of yellow plaque with the increase of thrombogenic potential; therefore, where yellow plaques are newly formed they may increase the potential for thrombosis in DES. The formation of yellow neointima was not associated with the use of dual antiplatelet therapy at follow-up.

Because both the stent itself and yellow plaque have thrombogenic potential, exposure of either

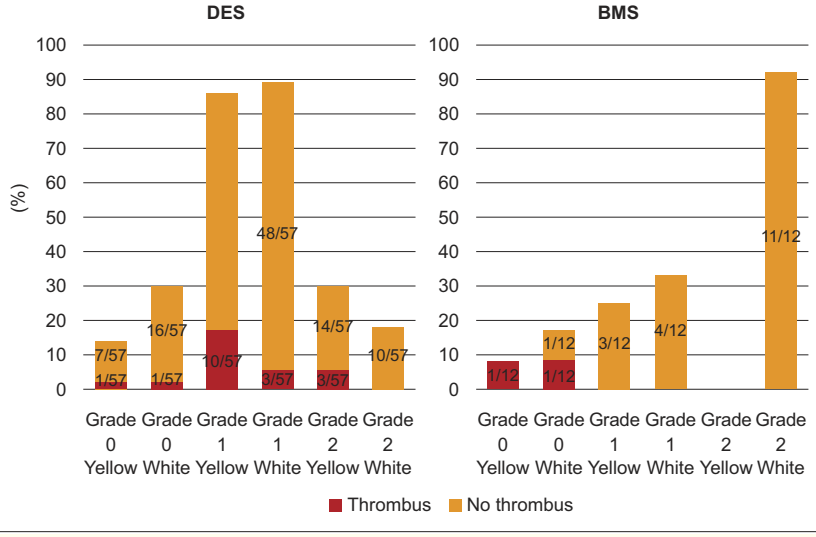

Figure 3. Incidence of Each Status of Neointima After DES and BMS Implantation at Follow-Up

Status of neointima was defined by the combination of neointima coverage (Grade 0 to 2), lesion color (white or yellow), and thrombus (presence or absence). Incidence of each neointima status among all drug-eluting stents (DES) or bare-metal stents (BMS) was presented. Because each stent may have multiple incidences of neointima, summation of the incidences of all neointima is >100%. DES was covered mainly by Grade-1 neointima; BMS was covered mainly by Grade-2 neointima. Yellow Grade-2 neointima (newly formed over stent) was detected in 30% of lesions in DES, but was never detected in BMS. Thrombus was detected on yellow and/or Grade-0/1 neointima, but was never detected on white Grade-2 neointima.

component would increase the thrombogenic potential of the lesion. Indeed, in the present study (Fig. 3), thrombus was detected where stent was not covered by neointima (Grade 0) or where yellow plaque was present at the lesion. Grade-1 neointima formed over DES may be inadequate to reduce the thrombogenic potential of the stent itself or may have thrombogenic potential itself, because thrombus was detected in areas DES was covered by white Grade-1 neointima. Although both poor stent coverage (Grade 0 or 1) and yellow color were risk factors for thrombus formation, the odds ratio of thrombus formation was higher for yellow (vs. white) lesions than for lesions with Grade-0/1 (vs. Grade-2) stent coverage (18.2 [95% confidence interval: 2.3 to 144.1] vs. 5.3 [95% confidence interval: 1.4 to 19.8]), so yellow color appears to be more contributory to thrombus formation than poor stent coverage. It should be noted that thrombus was not detected when stent struts were buried under a white neointima (white Grade-2 neointima). This situation potentially represents the ideal state of vascular healing after stent implantation. However, these findings need to be validated in a large cohort of patients in future studies.

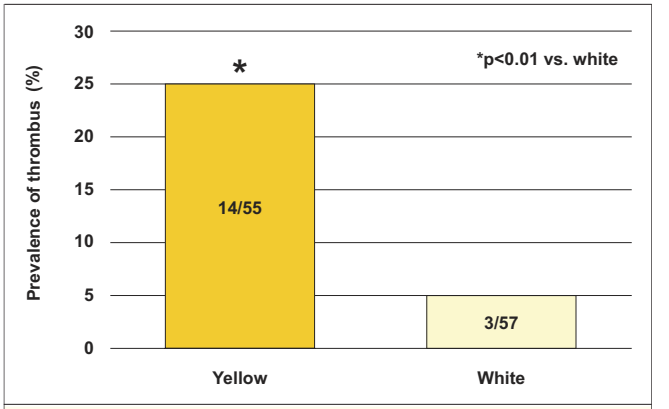

Figure 4. Lesion Color and Prevalence of Thrombus on DES-Implanted Lesions

Thrombus was detected significantly more often on the yellow area than on the white area at follow-up after drug-eluting stent (DES) implantation.

Finn et al. (29) previously reported in histologic studies that a lack of endothelial strut coverage is the single best correlate of late stent thrombosis. Since re-endothelialization after DES implantation is impaired, it is likely that lipid transport into the neointima is enhanced and therefore may result in early atherosclerotic changes such as foam cell formation with progression of atherosclerosis. Newly formed athero-

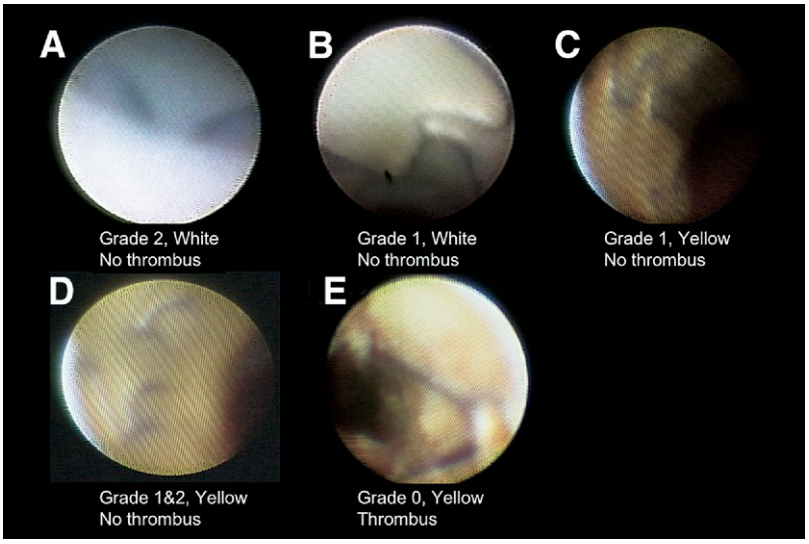

Figure 5. Grading Scheme of Angioscopic Evaluation

(A) A case of a drug-eluting stent (DES) well covered by white smooth neointima (Grade 2) without yellow plaque or thrombus. Stent is partially seen through neointima but was below the level of the neointima surface. **(B)** A case of DES with a thin layer of neointima (Grade 1). Yellow plaque or thrombus was not detected. Stent was seen above the level of the neointima surface. **(C)** A case of DES with a thin layer of neointima (Grade 1). Yellow plaque was detected in the original vessel wall underneath the stent, but thrombus was not detected. Stent was seen above the level of the neointima surface. **(D)** A case of DES with partially invisible coverage by yellow neointima (Grade 2). No thrombus was observed. **(E)** A case of a thrombus on the yellow plaque under the DES, which was not covered by neointima (Grade 0).

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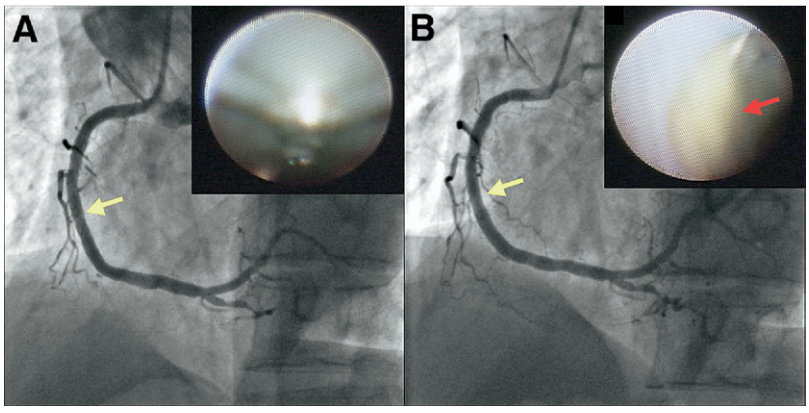

Figure 6. A Representative Case of Yellow Neointimal Formation Over DES

A 64-year-old man with silent myocardial ischemia received percutaneous coronary intervention (PCI) with a Cypher stent (3.5 × 23 mm) in the mid right coronary artery **(yellow arrows)**. He had hypercholesterolemia but not hypertension or diabetes mellitus. Angiographic and angioscopic images immediately after stenting **(A)** and at 12-month follow-up **(B)** are presented. The stent was covered by yellow neointima (Grade 2, **red arrow**) at 12-month follow-up. DES = drug-eluting stent.

sclerotic lesions will eventually result in necrotic core formation from death of infiltrated macrophages through apoptosis followed by thin fibrous cap formation, which may rupture and lead to luminal thrombosis (30).

Study limitations. In this study, we examined only sirolimus-eluting stents; therefore the results of this study cannot be applied to other DES. The patients who underwent angioscopy received heparin, aspirin, and ticlopidine, but not clopidogrel or glycoprotein IIb/IIIa inhibitors, so the impact of the latter drugs was not assessed. It is unknown if the angioscopically defined thin layer of neointima consists of a few layers of smooth muscle cells or a layer of endothelial cells and also if the neointima has mature endothelial function. Using angioscopy, we can, however, evaluate the antithrombogenic function of the layer by the absence or presence of thrombus on the surface. There are some limitations in the angioscopic observations. Imaging is limited to the surface of the coronary lumen. It is also difficult to evaluate the angioscopic findings quantitatively, thus the yellow gradation of plaque and neointimal stent coverage was evaluated using a very discontinuous semiquantitative scoring system. Anatomic complexity such as a tortuous and angulated vessel may have limited a complete circumferential view of the vessel. Because we performed

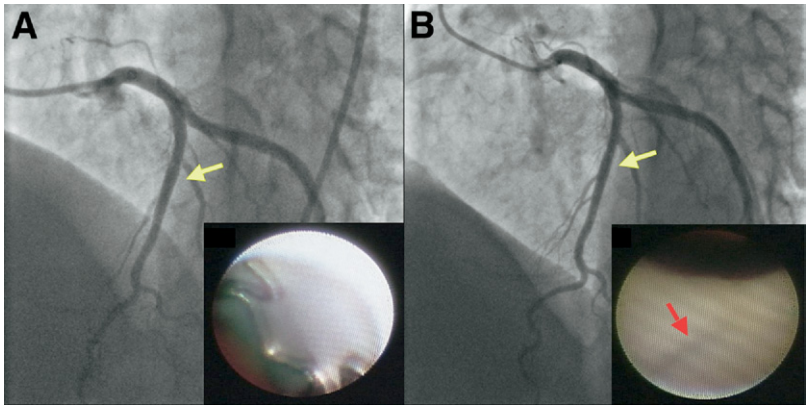

Figure 7. A Representative Case of Yellow Neointima Formation Over DES

A 44-year-old man with stable effort angina received percutaneous coronary intervention (PCI) with Cypher stent (3.5 × 18 mm) in the proximal left anterior descending coronary artery **(yellow arrows)**. He had hypercholesterolemia but did not have hypertension or diabetes mellitus. Angiographic and angioscopic images immediately after stenting **(A)** and at 12-month follow-up **(B)** are presented. Stent was covered by yellow neointima (Grade 2, **red arrow**) at 12-month follow-up.

follow-up at only one point in time, further changes in the appearance of neointima are left to be clarified by the repeated follow-ups. The relationship between angioscopically detected thrombogenic lesion and the risk of stent thrombosis as a clinical event needs to be demonstrated in a prospective long-term study and with a larger sample size.

CONCLUSIONS

Sirolimus DES show poor neointimal coverage and promote formation of yellow plaque in the stented lesions at 10-month follow-up. The yellow areas were associated with an increased incidence of mural thrombus, and complete coverage with white neointima was not, suggesting a higher risk of stent thrombosis in newly formed yellow lesions after sirolimus DES implantation.

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